MEDICATIONS TO TREAT DIABETES MELLITUS

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*No disclosures

OBJECTIVES

- EXPLAIN THREE DIFFERENCES BETWEEN DPP-4 INHIBITORS AND GLP-1 AGONISTS
- STATE AT LEAST TWO MEDICATIONS THAT CAN BE USED TO TREAT PRE-DIABETES PATIENTS
- DESCRIBE THE MECHANISM OF ACTION OF SGLT-2 INHIBITORS
- LIST 3 CHARACTERISTICS OF A DRUG THAT WOULD BE IDEAL IN TREATING TYPE 2 DIABETES
- LIST 2 TYPES OF MEDICATIONS EXPECTED TO BE APPROVED TO TREAT DIABETES WITHIN THE NEXT YEAR

History of Diabetes Care

- RKC Hx: Diagnosed 11-7-1949, 64 years ago
- 3 Cornerstones of diabetes treatment: Nutrition, Exercise, Medications
- All treatments are unsuccessful unless patient is adherent, motivated and well educated (EMPOWERED)
- Most cost effective treatment (best outcomes for the price) are meds or a combination of medications
- New trends include combination therapies, identifying & treating pre-diabetes, & treating cardiovascular risk factors in addition to managing blood glucose levels

Significant Developments in DM

- SMBG
- HbA1C
- Sugar Free Beverages
- Purer Insulins/Basal-Bolus Insulin Treatment
- Diabetes Education as a specialty
- Sharper, shorter needles
- Numerous new classes of medications-Now have 13 for type 2 DM
- Insulin Pumps and CGM
- Awareness/Proof that Hyperglycemia=Complications (DCCT)
- Diabetes Equals CVD
- Explosion of type 2 DM worldwide
- Patient Centered Approach for diabetes patients who get access to care
- Emphasis on Pre-Diabetes & Prevention of Type 2 DM
- Now 382 million with diabetes worldwide at cost of $ 548 billion

Barriers To Normalizing BG

- DENIAL
- COMPLEXITY OF TREATMENTS & Health care system
- ADHERENCE—note that texting improves adherence
- FEAR OF WEIGHT GAIN/HYPOGLYCEMIA
- ACCESS TO CARE, LANGUAGE, CULTURAL & LITERACY CHALLENGES ARE ALL MAJOR OBSTACLES TO CARE
- EXPENSE, HEALTH CARE ISSUES
- ACUTE HEALTH CARE SYSTEM VS. CHRONIC DISEASE CARE
- LACK OF HEALTH CARE PROVIDER TRAINING SPECIFICALLY ABOUT DIABETES
- GENETIC FACTORS
- LACK OF PERSONALIZATION OF DIABETES TREATMENT
CARE OF DIABETES PATIENTS IS A NATIONAL DISGRACE

Status of Diabetes Management

- Majority of patients with type 2 diabetes have only fair to poor metabolic control
  - fasting serum glucose levels of ≥ 200 mg/dL
  - HbA1c levels of 8.0 % or Greater in over half of patients
  - Why are only 27% of type 1’s on a pump?
  - Type 2 Diabetes is Exploding in incidence
  - Postprandial blood glucose levels average ~300 mg/dL
  - < 2% of American adults with diabetes receive optimal quality of care
- Outcome research is showing improvement. YEAH!

References:
Cowie CC et al. Diabetes in America. 2nd ed.
ADA Standards of Care

- Physician Visits: 2-4 per year
- HbA1c Measurement: 2-4 per year
- Fasting Glucose Measurement (SMBG): 4-6 per year/daily
- Foot Exams: Every Visit
- Aspirin?, ACE-I or ARB, Statins: Daily
- Urine Protein Measurements: Yearly
- Blood Pressure: As needed to achieve goal
- Lipid Levels: As needed to achieve goal
- Dilated Pupil Eye Exam, dental care: Yearly
- Flu, Pneumovax & Shingles Vaccines: As needed
- Education, Nutrition, Exercise: As needed
- HOW MANY OF THESE COULD BE DONE AT WORK???

Ideal Medication for Diabetes

- SAFE AND EFFECTIVE
- TAKEN ORALLY
- NO WEIGHT GAIN
- NO HYPOGLYCEMIA
- NO INCREASED INCIDENCE OF CANCER, HEART DISEASE, PANCREATITIS, OSTEOPOROSIS, ETC.
- NO INTERACTIONS WITH OTHER NEEDED MEDICATIONS
- SIMPLE TO USE; NO COMPLICATED DIRECTIONS FOR USE
- LOW COST (GREAT COST BENEFIT/RATIO)

TYPE 1 DM MEDS

- INSULIN: Basal-Bolus; syringe injections or pen or insulin pump or hopefully pulmonary
- HYPOGLYCEMIA: GLUCAGON, GLUCOSE TABS
- ASPIRIN?
- STATIN?
- ACE INHIBITOR OR ARB OR OTHER BP MED?
- MICRONUTRIENTS?: Mg, Vit D, CoQ10, Zinc, B Vitamins, Alpha Lipoic Acid, Other?
- COMPLICATION’S TREATMENTS: Neuropathy, Retinopathy, Nephropathy, ED, Infections, Foot care, Dental care, many others..
- Flu Shot, Pneumovax, Shingles vaccination

What would you Prescribe?

- Insure a 63 y.o. Hispanic male with an A1C of 9% who is overweight, has high BP, high Lipids, does not exercise and eats at least 3X daily plus snacks walks into your practice....
- Besides putting him on CV meds, an exercise program and referring him to an RD, WOULD YOU?: a) put him on basal-bolus insulin? b) Put him on metformin, pioglitazone and an injection of liaramglutide daily? c) try him on Dapaglifozin plus metformin and Linagliptin? d) None of the above? e) Any of the above are reasonable!

*After checking with an attorney…….

Meds for Type 2 DM

- 13 CLASSES OF M EDs FOR TYPE 2 DM
- INSULINS: Just Basal? Basal-Bolus? Just Bolus (meal time)? Pens, pumps, syringes?
- OTHER INJECTABLES: GLP-1 AGONISTS, AMYLIN
- ORAL AGENTS: Sulfonylureas, Metformin, TZD’s, Alpha-glucosidase inhibitors, Meglitinides, DPP-4 Inhibitors, SGLT-2 Inhibitors, Bile Acid Sequestrants, Bromocriptine
- HYPO TREATMENTS?
- BP TREATMENTS; STATIN THERAPY; ASPIRIN?
- NUMEROUS MEDS TO TREAT COMPLICATIONS
- MICRONUTRIENTS? VACCINATIONS

13 Classes of Antihyperglycemic Agents Available for Treatment of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Class</th>
<th>4D Indicator</th>
<th>Fasting</th>
<th>PP</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Drug Interactions</th>
<th>Outcome Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>None</td>
<td>None</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>18-28</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1.8</td>
<td>1.8</td>
<td>DIGAMI, UKPDS (DCCT)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>6-14</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1.4</td>
<td>1.4</td>
<td>TECOS, PROactive, NAVIGATOR</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>54-64</td>
<td>Fasting</td>
<td>No</td>
<td>Gain</td>
<td>1</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Dapaglifozin</td>
<td>1-16</td>
<td>Fasting</td>
<td>No</td>
<td>Gain</td>
<td>2</td>
<td>2</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>16-18</td>
<td>Fasting</td>
<td>No</td>
<td>Gain</td>
<td>3</td>
<td>3</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>16-18</td>
<td>Fasting</td>
<td>No</td>
<td>Gain</td>
<td>3</td>
<td>3</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>58-10</td>
<td>PP</td>
<td>No</td>
<td>Loss</td>
<td>2</td>
<td>2</td>
<td>NAVIGATOR</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>58-10</td>
<td>PP</td>
<td>No</td>
<td>Loss</td>
<td>3</td>
<td>3</td>
<td>NAVIGATOR</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>58-10</td>
<td>PP</td>
<td>No</td>
<td>Loss</td>
<td>2</td>
<td>2</td>
<td>NAVIGATOR</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>58-10</td>
<td>PP</td>
<td>No</td>
<td>Loss</td>
<td>3</td>
<td>3</td>
<td>NAVIGATOR</td>
</tr>
<tr>
<td>Dapaglifozin</td>
<td>4-6</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>1.2</td>
<td>1.2</td>
<td>None</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>6-7</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

**Major Pharmacological Targets in T2DM**

- Pancreas (β-cell dysfunction)
- Muscle and fat (Glucose level)
- Liver (Hepatic glucose overproduction)
- Gut (DPP-4 inhibitors; TZDs; incretin mimetics; Pramlintide)

**β-Cell Decline in T2DM**

- β-Cell Function (%)
- Years From Diagnosis

**Antidiabetic Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Available Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide, Glimeperide, Glipizide</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone, Rosiglitazone</td>
</tr>
<tr>
<td>α-glucosidase Inhibitors</td>
<td>Acarbose, Miglitol</td>
</tr>
<tr>
<td>Glitizides</td>
<td>Repaglinide, Nateglinide</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Sitagliptin, Saxagliptin, Linagliptin, Aloglipin</td>
</tr>
<tr>
<td>Bile Acid Sequestrant</td>
<td>Colesevelam (Welchol)</td>
</tr>
<tr>
<td>Dopamine Agonist</td>
<td>Bromocriptine (Cycloset)</td>
</tr>
</tbody>
</table>

**Antidiabetic Agents Continued**

<table>
<thead>
<tr>
<th>Class</th>
<th>Available Injectable Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Many</td>
</tr>
<tr>
<td>Incretin Mimetics</td>
<td>Exenatide, Liraglutide</td>
</tr>
<tr>
<td>Amylin Analogue</td>
<td>Pramlintide (Symlin)</td>
</tr>
</tbody>
</table>

**Sulfonylureas**

- Mechanism of action
  - Insulin secretagogues
  - Increase basal and meal-stimulated insulin secretion
- In patients who respond to sulfonylureas, these agents can:
  - Decrease fasting plasma glucose by ~60-70 mg/dL
  - Decrease A1C by 1% to 2%

**Sulfonylureas: Second-Generation Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose (Brand)</th>
<th>Max Dose (mg/day)</th>
<th>Frequency (times/day)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide (Diabetes or Micronase)</td>
<td>2.5-5 mg/day</td>
<td>20 mg/day</td>
<td>1 or 2</td>
<td>12-24</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1-2 mg/day</td>
<td>8 mg/day</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Glipizide (Glycinol)</td>
<td>5 mg/day</td>
<td>40 mg/day</td>
<td>1 or 2</td>
<td>12-24</td>
</tr>
<tr>
<td>Glyburide-Micronized (Glynase)</td>
<td>1.5-3 mg/day</td>
<td>12 mg/day</td>
<td>1 or 2</td>
<td>12-24</td>
</tr>
</tbody>
</table>
Patient Response to Sulfonylureas

60% – 70% of patients with type 2 diabetes respond initially.
Patients most likely to respond:
- Onset of diabetes after age 30
- Diagnosed for less than 5 years
- Normal weight or obese
- No prior use of insulin or < 40 u/day
Annually, ~5% of initial responders experience secondary failure as beta cell function declines.

Sulfonylureas: Adverse Drug Reactions

- Hypoglycemia
- Weight gain (secondary to increased insulin release)
- Falling out of favor but still used due to being cheap
- Other ADRs
  - Gastrointestinal
  - Skin rashes
  - Hepatic changes (rare)

Meglitinides/Phenylalanines

- Mechanism of action:
  - Insulin secretagogues
- Chemically unrelated to sulfonylureas:
  - Repaglinide is a benzoic acid derivative
  - Nateglinide is a d-phenylalanine derivative

Meglitinides: Dosage

<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Initial Dose</th>
<th>Max Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide (Prandin)</td>
<td>0.5 mg or 1-2 mg if A1C &gt;8 (15 min. before meals)</td>
<td>16 mg</td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>60-120 mg TID (1 to 30 min. before meals)</td>
<td>120 mg before meals</td>
</tr>
</tbody>
</table>

Meglitinides: ADRs

- ADRs associated with both agents
  - Hypoglycemia
  - Weight gain (due to increased insulin secretion)
- Other ADRs for repaglinide
  - GI disturbances
  - Upper respiratory infection or problems
  - Arthralgia
  - Headache
- Other ADR for nateglinide
  - Dizziness

Meglitinides/Phenylalanines

- Advantages: None really
  - Both drugs result in lower insulin exposure and potential for hypoglycemia
  - Dose must be omitted if a meal is skipped
- Disadvantages
  - Compliance may be problematic due to multiple daily dosing (up to 3-4 times per day)
  - Patients having a poor response to sulfonylurea therapy are not likely to respond if these drugs are added
  - High cost; seldom used
Biguanides

Metformin (Glucophage) is the only agent in this class
Improves insulin sensitivity by reducing insulin resistance:
  - Decreases hepatic glucose production (primary action)
  - Increases skeletal muscle glucose uptake (secondary action)
  - Decreases intestinal absorption of glucose (minor effect)

MOST USED MEDICATION TO TREAT TYPE 2 DM

Metformin: Dosage

- Take with meals
- Start with small dose (500 mg) for less GI problems
- Increase dose at weekly intervals (or longer)
- Maximum dose:
  - 2000 mg (effective)
  - 2550 mg/day (FDA-approved)
- Given 2 to 3 times a day (immediate release)
- Once a day extended release products (Glucophage XR) available

Metformin: Advantages

- May aid weight loss or weight maintenance
- Improves plasma lipids
  - Decreased triglycerides
  - Decreased LDL-cholesterol
- Lowers insulin levels (indirect effect)
- Usually does not cause hypoglycemia
- BEING USED TO PREVENT CANCER

Metformin: Concerns

- ADRs can lessen tolerability
  - GI-related complaints (diarrhea, nausea, vomiting)
  - Unpleasant or metallic taste
- Lactic acidosis is a serious, rare event
  - 0.03 cases/1000 patient-years
  - Cases have 50% mortality rate
- Reduction in serum vitamin B12 levels (rarely associated with anemia)

Metformin and B12 Deficiency

- Malabsorption of B12 in ~30% of metformin users
  - B12 not absorbed in the terminal ileum
    - Metformin effect on calcium-dependent membrane action
    - Dose- and treatment duration-dependent
  - Takes 12-15 years to totally deplete B12 stores
    - On the verge of an epidemic?

Recommendations:

- Calcium supplementation?
- Annual B-12 level?
- Annual 1000 mcg injection of B12?
Metformin: Contraindications
- Avoid/Cautious use in:
  - Pregnancy or lactation
  - Congestive heart failure
  - Hepatic dysfunction
  - History of alcohol abuse or binge drinking
  - Tissue hypoxia (e.g., acute MI, dye tests)
  - Renal dysfunction
    - Serum creatinine >1.5 mg/dL in men
    - Serum creatinine >1.4 mg/dL in women
  - Age >80 years (without adequate renal function or creatinine clearance)

PRE-DIABETES
- NOW A RECOGNIZED CONDITION
- 74 TO 90 MILLION POTENTIAL PATIENTS IN THE U.S.
- MEDICATIONS TESTED TO TREAT INCLUDE: ACARBOSE, METFORMIN
- BEST TREATMENTS INCLUDE LIFE STYLE CHANGES: EXERCISE & IMPROVED NUTRITION
- DeFRONZO USES METFORMIN, ACTOS AND A GLP-1 AGONIST WITH GREAT RESULTS

Thiazolidinediones
- Directly reduces insulin resistance by activating PPAR-gamma nuclear receptors
  - Increase glucose uptake in skeletal muscle and fat cells
  - Lower hepatic glucose output

Thiazolidinediones: Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Max Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (Actos)</td>
<td>15 or 30 mg qd</td>
<td>45 mg</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>4 mg qd (BID)</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

Thiazolidinediones: ADRs
- Weight gain of 1-6 kg, which is dose dependent and varies with the type of agent used in combination therapy
- Peripheral edema, which tends to be dose dependent, more common in patients treated concomitantly with insulin, and may cause dyspnea and potentiate heart failure
- Macular edema
- Increased incidence of bone fractures

Thiazolidinediones
- Usual reduction in A1C of 1.5% - 2.5%
- Decreases in blood glucose can be seen within 2-4 weeks
- Maximum glucose lowering effects may take up to 12 weeks
- Demonstrated perseverance of effect for up to 1-2 years
- Initial liver concerns were shown to be unlikely
Rosiglitazone REMS: 2011 Update

Avandia-Rosiglitazone Medicines Access Program
- After November 18, 2011, rosiglitazone will no longer be available in retail pharmacies
- HCPs and patients must be enrolled to prescribe or review rosiglitazone products
- People can receive rosiglitazone by mail order through certified pharmacies
- THIS WAS REVERSED IN DECEMBER 2013; BUT FEW PRESCRIBERS EXPECTED TO PRESCRIBE IT


α-Glucosidase Inhibitors

- Mechanism of action:
  - Inhibit membrane-bound α-glucosidase enzymes in small intestine
  - Decrease glucose absorption from intestine, reducing postprandial hyperglycemia
- Two agents in this class:
  - Acarbose (Precose)
  - Miglitol (Glyset)

α-Glucosidase Inhibitors: Dosage

<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Initial Dose</th>
<th>Maintenance Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose (Precose)</td>
<td>25 mg TID</td>
<td>50 or 100 mg TID</td>
<td>50 mg TID (patients ≤60 kg)</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>25 mg TID</td>
<td>50 or 100 mg TID</td>
<td>100 mg TID (patients &gt;60 kg)</td>
</tr>
</tbody>
</table>

Dosages should be taken with first bite of meal

α-Glucosidase Inhibitors: Adverse Drug Reactions (ADRs)

- GI ADRs are most common
  - flatulence (up to 77%)
  - diarrhea (up to 33%)
  - abdominal pain (up to 25%)
- GI ADRs tend to diminish with time
- can be minimized by starting with a low dose, then gradually titrating upward
- limiting foods high in sucrose also may lessen GI ADRs
- Note: Because sucrose digestion is slowed, use honey or glucose tablets to treat hypoglycemia, not table or brown sugar

α-Glucosidase Inhibitors: Contraindications

1. Inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction, and those predisposed to intestinal obstruction
2. Chronic intestinal diseases associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine
**Bile Acid Sequestrant**
- Colesevelam (Welchol) is approved for treatment of type 2 diabetes
- Lowers LDL Cholesterol
- Lowers A1C by about 0.5%

**Common Side Effects:**
- Constipation
- Nausea
- Dyspepsia
- Increases in triglycerides
- Contraindicated in patients with triglyceride levels > 500 mg/dL
- History of bowel obstruction due to constipation

**Bromocriptine (Cycloset)**
- Approved in 2009 by FDA to treat T2DM
- Once daily in AM with food and is a quick release, low dose (0.8 mg) formulation
- Acts on CNS to improve insulin resistance and glucose tolerance – resets neuroendocrine rhythms

**INCRETINS**
- GLP-1 AGONISTS: Exenatide & Liraglutide
- DPP-4 INHIBITORS: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin

**Incretins play an important role in glucose homeostasis**
- Release of gut hormones—Incretins
- Incretin mimetics and DPP-4 inhibitors: differences and similarities

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**Incretin mimetics and DPP-4 inhibitors: differences and similarities**

<table>
<thead>
<tr>
<th>Incretin mimetics</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of stimulation of insulin secretion exclusively through GLP-1 effect</td>
<td>Yes</td>
</tr>
<tr>
<td>Restimulation of insulin secretion (2 phases)</td>
<td>Yes (exenatide)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No</td>
</tr>
<tr>
<td>Maintained counter-regulation by glucagon in hypoglycaemia</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect on body weight</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, Vomiting, Diarrhea</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>

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**Incretin mimetic** – mimics the action of GLP-1 (glucagon-like peptide – 1)

- Exenatide is a *synthetic version* of a salivary protein from the Gila monster (Exendin-4)
- Binds to GLP-1 receptors but is resistant to degradation by DPP-IV

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**Exenatide LAR (Bydureon)**

- Once-weekly administration
- Consists of microspheres
  - Exenatide within a poly(lactide-coglycolide) matrix
  - Following injection exenatide is slowly released from the microspheres via diffusion and erosion

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**Liraglutide (Victoza)**

- Long-acting, synthetic analog of human GLP-1
- Approved by the FDA in January 2010

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**GLP-1 Agonists: pancreatitis data**

- Pancreatitis in clinical trial program:
  - 7 cases of pancreatitis in participants receiving liraglutide; 6 in exenatide
  - Believed that all patients had predisposing issues
  - No higher incidence than in general population
  - L. Olansky in *Cleveland Clinic Journal of Medicine* August 2010 vol. 77 8 503-505 concluded that there is not an increased risk of acute pancreatitis in Incretin users and that pancreatitis is known to be higher in DM patients
  - ADS ON TV DO HAVE PATIENTS ALARMED
Incretin Mimetics: Thyroid Cancer?

Preclinical data from rodent models linked GLP-1 agonists with dose-dependent and treatment-duration-dependent thyroid C-cell tumors. Benign C-cell adenomas observed in animal studies at plasma drug levels similar to those seen in humans at approved doses GLP-1 receptors present in rodent C-cells, but not demonstrable in human C-cells. Incidence of medullary thyroid cancer ~600 cases per year, thus unlikely to see a signal in clinical studies. Note again that the lawyers have ads on TV.


DPP-4 Inhibitors

- TAKEN ORALLY, FEW SIDE EFFECTS
- NO WEIGHT LOSS
- BLOCKS ENZYME THAT BREAKS DOWN GLP-1
- USUALLY USED IN COMBINATION WITH METFORMIN OR OTHER DM MEDS
- EXPENSIVE IN TERMS OF IMPACT ON DECREASING A1C

Sitagliptin: Dosing

Usual Dosing for Sitagliptin

<table>
<thead>
<tr>
<th>100 mg once daily</th>
<th>50 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>With or without food</td>
<td>Moderate CRCl &gt;50 mL/min (&lt;Serum Cr levels [mg/dL]: Men: &gt;1.7 –≤3.0; Women: &gt;1.5 –≤2.5)</td>
</tr>
</tbody>
</table>

Assessment of renal function is recommended prior to initiation and periodically thereafter.

1^Patients with mild renal insufficiency—100 mg once daily.
1^ESRD=end stage renal disease requiring hemodialysis or peritoneal dialysis.

Sitagliptin (Januvia)

- Adverse Effects
  - Adverse Reactions reported in ≥5% of patients and more commonly than in patients given placebo, regardless of investigator assessment of causality: upper respiratory tract infections, nasopharyngitis, and HA.
  - First DPP-4 Inhibitor and still has about 90% of the market

Sitagliptin (Januvia) and Pancreatitis?

Prescribing information revised in September 2009 for sitagliptin (Januvia) and sitagliptin/metformin (Janumet)

FDA cited 88 cases of acute pancreatitis reported between October 2006 and February 2009

2 cases of hemorrhagic or necrotizing pancreatitis

Recommendations from FDA

- Monitor patients carefully for pancreatitis after initiation of therapy or dose increases
- Use cautiously and with appropriate monitoring in patients with a history of pancreatitis

Recent controversial summary of data shows a lack of cause/effect: No greater incidence than in general population; LAWYERS STILL HAVE ADS THOUGH!!

Saxagliptin (Onglyza)

- Saxagliptin has a half-life suitable for once-daily oral administration
- Saxagliptin appears to be weight neutral
- Saxagliptin reduces A1C by 0.5-1%
- The most common AEs are headache, upper respiratory tract infection, urinary tract infection, nasopharyngitis, arthralgia, nausea and cough.
Linagliptin (Tradjenta)

• FDA approved May 2011
• Weight neutral; similar A1C reductions to others
• Availability & Dosing:
  – Linagliptin 5mg QD
  – Studied in patients with varying degrees of renal impairment
    • Change in exposure in those with RI not thought to be clinically significant
    • No DOSE ADJUSTMENTS NEEDED based on renal function

Graefe-Mody et al. Diabet Ocyt Metab. 2011
Munch L et al. Diabetes. 2011
Linagliptin Prescribing Information.

Alogliptin (Nesina)

• FDA approved January 2013
• ME TOO DPP-4 Inhibitor
• Availability & Dosing:
  – Alogliptin 6.25, 12.5 and 25 mg tablets
  – Dosing: 25 mg once daily
    • Renal dosing:
      – CrCl 30-59 ml/min: 12.5 mg once daily
      – CrCl < 30 ml/min: 6.25 mg once daily
  – Alogliptin + Metformin (Kazano)
    • 12.5mg/500mg OR 12.5mg/1000mg
  – Alogliptin + Pioglitazone (Oseni)
    • 12.5-25mg/15-30/45mg

Linagliptin Prescribing Information.

Amylin: a β-cell hormone

• First reported in 1987
• Important regulator of glucose influx into bloodstream; released when insulin is released
• 37–amino acid neuroendocrine hormone

Physiological role of amylin

• Regulates the appearance of glucose from the meal in the circulation:
  – Slowed gastric emptying
  – Suppression of postprandial glucagon secretion
  – Reduced food intake
• People with diabetes are amylin deficient
  – Relative deficiency in type 2 diabetes
  – Absolute deficiency in type 1 diabetes


Pramlintide (Symlin®)

• Pramlintide (Symlin®) is a synthetic amylin analog that mimics the action of amylin
  = amylinomimetic

Pramlintide sites of action

CNS: Promotes satiety
Liver: Reduced hepatic glucose output
Stomach: Slowing of gastric emptying
Alpha cell: Inhibition of glucagon secretion

Pramlintide counseling points

- Pramlintide is best injected in the abdomen or the thigh. Variable absorption when injected into arm.
- Unit conversion for U-100 insulin syringe (30 Unit syringe recommended) from vial:
  - 15mcg = 2.5 units
  - 30mcg = 5 units
  - 45mcg = 7.5 units
  - 60mcg = 10 units
  - 120mcg = 20 units
- Vial concentration (600 mcg/mL) not the same as pen (1000 mcg/mL)
- Side effects have caused it to used only rarely.

Sodium Glucose Cotransporter 2 (SGLT-2) Inhibition

90% of filtered glucose is reabsorbed through SGLT2 transporters in the early proximal tubule. 10% is reabsorbed by SGLT1 transporters in the late proximal tubule. Inhibition of SGLT2 transporters in the proximal tubule blocks the reabsorption of filtered glucose = increased glucose excretion via urine.

SGLT-2 Inhibitor Developmental Pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lead Company</th>
<th>Phase</th>
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<tr>
<td>Dapagliflozin</td>
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<tr>
<td>Canagliflozin</td>
<td>Johnson &amp; Johnson</td>
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<td>Boehringer Ingelheim</td>
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<td>ISIS-SGLT2Rx</td>
<td>Isis Pharmaceuticals</td>
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</table>

SGLT-2 Inhibitors: Potential Pros and Cons

- Potential Pros:
  - Unique non-insulin-dependent MOA
  - Potentially useful in T2DM and T1DM
  - Potential weight loss
  - Decrease in BP
  - Low risk of hypoglycemia as monotherapy
- Potential Cons:
  - Increased CA risk? Doubtful
  - Hepatotoxicity risk?
  - Risk of UTI/Genital infections
  - Exacerbation of urinary urgency?
  - Cost?

FUTURE DIABETES MEDS

- AFREZZA-Pulmonary Insulin from Mannkind
- INSULIN DEGLUDEC (TRESIBA) from NovoNordisk
- Over 90 meds in research
- Check out: Mejuddar SK, Inzucchi SE. Investigational Anti-hyperglycemic agents: the future of Type 2 Diabetes drugs. Endocrine (2013) 44:47–58

A Blast (Bust) From the Past
Technosphere Insulin: 
AFREZZA

Technosphere Insulin: Pharmacokinetics

Technosphere Insulin: Pros and Cons

Technosphere Insulin
- Potential Pros:
  - Prandial coverage without injection
  - “Very” rapid acting insulin
  - Less weight gain?
  - Less hypoglycemia?

- Potential Cons/Considerations:
  - Use in smokers/COPD?
  - Respiratory ADEs
  - Usability?
  - Acceptance?
  - Price?

Insulin Degludec (Tresiba)
- Ultra-long acting basal insulin (half-life of 25 hours and DOA of over 40 hours)
- Has the potential to be used less than once daily
- Demonstrated efficacy in both type 1 and type 2 diabetes
- Lower hypoglycemia when compared to insulin glargine when used once daily (in some studies)

Predictions from an old PWD
- Incretins will continue to be used more often
- CGM will become more popular with smaller and easier to use sensors
- Combination Therapies will be the NORM
- Technology will continue to explode and change how we live
- Newer treatments will be approved (over 90 diabetes meds being investigated)
- Combination insulin/Glucagon pumps with CGM will be developed

More Predictions
- More patients will take Vitamin D, Magnesium, and other vitamins & antioxidants
- More patients will use unproven Natural Products without much impact
- Patients will pay more for health care if they smoke or follow other unhealthy habits
More Predictions

- The more we know, the more we know that there is so much more to know
- A Major area of diabetes research will focus on Oxidative Stress, Inflammation and Obesity
- Watch the medical literature for articles on:
  - Relaxin, Beige Fat/Irisin, Biomarkers for kidney disease & other complications, new treatments, TB Vaccine for type 1’s; statins decrease death by 50% and decrease pancreatitis; Genome research will explode; Postprandial glucose reduction (flat sugars) will be emphasized.

Thank you!

THANK YOU AGAIN!!!

- QUESTIONS ???????????
- COMMENTS !!!!!!!
- CONTACT: rkamp@wsu.edu